REMARKS

Claims 35-50, 52, 63, 64 and 68-72 have been examined. Claims 53-56 and 65-67 have been withdrawn. Claims 35 and 40 have been amended to correct inadvertent clerical errors. Claims 37, 42, 46, 47, 69 and 71 have been amended to better claim the invention. None of the amendments made herein constitutes the addition of new matter.

The Invention

Applicants respectfully provide the following expanded discussion of the claimed invention to facilitate the discussion of the rejections and to make clear the basis of the invention as claimed.

Note that in nature, the binding of the HIV gp120 (Env protein) to the CD4 receptor results in a conformation change in the gp120 such that the V3 loop of gp120 is exposed. The V3 loop thus exposed can then interact with other cell surface receptors for HIV, including chemokine receptors CCR5 and CXCR4 (pg. 1 of Specification). Note that there are HIV strains that infect cells via these chemokine receptors. Other cryptic epitopes are formed during the infection process as interactions continue to occur. The Specification further states that the cryptic epitopes have been the object of significant research in the vaccine arena. The V3 peptide is known to interact with CXCR4, and V3-specific antibodies reduce binding of V3 to CCR5.

By contrast, the Tat protein is a regulatory protein, involved in gene expression and virus replication. While Tat has long been recognized as an playing an important role in infection, it is the present inventors who have discovered that Tat interacts with the V3 loop of gp120 and have shown that this expands the ability of CCR5-troiphic viruses to infect cells which have naturally low levels of the CCR5 protein.

The present invention relates to the discovery that Tat binds to Env/gp120, **only** when the V3 loop is exposed. From this discovery flows the use of a Tat-gp120

complex for use an immunogen and in immunogenic compositions and methods. Consistent with the novelty of the present invention, the last paragraph of page 22 of the Specification discusses **novel** B cell epitopic determinants for the Tat/Env complex, formed via the V3 loop. Moreover, the data in the present application indicate that the TatΔV2 Env complex has the ability to strongly increase the antibody response to Env, while protecting anti-Tat antibody response as well, which are reduced when Env is administered. The use of the present Tat-V3 loop complexes as antigens is especially effective against HIV strains which bind the CCR5 receptor on host cells.

The Rejections under 35 U.S.C. 112, first paragraph

Claims 42, 47, 69 and 71 have been rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the requirement for written description. Applicants respectfully traverse this rejection.

The Patent Office has said that the rejection was made because the claims are interpreted as being drawn to a genus of peptides recited as fragment, mutants or variants thereof. The Patent Office has concluded that there is insufficient recitation of distinguishing identifying characteristics.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claims 42, 47, 69 and 71 to delete recitation of "fragment, mutants or variants thereof." It is believed that these amendments render the rejection moot. However, it is respectfully noted that critical portions of the relevant proteins, in reference to the Sequence Listing, had been recited. In view of the amendments to the claims, Applicants respectfully maintain that the requirements of the statute are met, and the rejection should be withdrawn.

The Rejections under 35 U.S.C. 112, second paragraph

Claims 42, 47, 69 and 71 have been rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

The Patent Office has alleged that the recitation of "fragment, mutant or variant thereof" renders the claims indefinite because one would not know what type of fragment, mutant or variant thereof would be immunogenic or capable of binding the specified residues of SEQ ID NO:1 or 2."

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have deleted the recitation of "fragment, mutant or variant thereof" from these claims. However, applicants respectfully note that the claims and the Specification clearly indicated critical structure and function that had been required.

In view of discussion in the present response and with the amendments to claims to better claim the invention, Applicants respectfully maintain on the record that the claims are sufficiently clear and definite as to fulfill the statutory requirements, in particular, in the eyes of the skilled artisan reader of the present application. Accordingly, the rejection under 35 U.S.C. 112, second paragraph, should be withdrawn.

The Rejections under 35 U.S.C. 103

Claims 35-50, 52, 63, 64 and 68-72 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Voss et al. (WO 01/54719) and further in view of Caselli et al. (1999) (J. Immunol. 162:5631-5638, Chang et al. (1999) Vaccine 17:1540-1548, Borbe et al. (1995) J. Peptide Science 1:109-123; Gzyl et al. (2004) Virology 318:493-506, Wyatt et al. (1995) J. Virology 69:5723-5733, Sattenau et al. (1993) J. Virology 67:7383-7393, Ibrahim et al. (1999) Virus Research 60:159-169 and Watanabe et al. (2000) Vaccine 19:1199-1203. Applicants respectfully traverse this rejection.

The Examiner has stated that the claims are directed to a complex comprising a first and a second peptide bound thereto, the first comprising the V3 loop of gp120, and wherein the V3 loop is exposed or available and thereby bound to a binding region on the second peptide to form the complex, second peptide comprising the

binding region which comprises at least residues 21-40 and 46-58 of the Tat protein set forth in SEQ ID NO: 1.

The claims are said not to recite the type of bond holding the components of the complex together. The Examiner has cited a passage in the Specification (p. 5) which appears to state that there is no need for stoichiometry of the components, and goes on to cite a passage related to binding interactions and the desirability of strengthening binding interactions, for example, with a disulfide bond. As to natural interactions, the Examiner has cited the Voss reference which refers to natural interaction between Tat and the V3 loop of gp120. The Patent Office conceded that Voss did not teach the Cys22 mutant, the use of the V3 loop as the first peptide, V2 deletion mutants, addition of CD4, heparin sulfate or the addition of other immune proteins or crosslinking the first and second peptides.

Applicants respectfully note that for there to be a complex between two peptides or proteins, each partner must be present or there can be no complex formed by binding of one to another. Thus, the claims are believed to provide sufficient specificity with respect to the complex that the Examiner's concern is moot. It is not believed that it should be necessary to specify a type of bond. It is a specific interaction that allows the complex to form, and as stated in the Specification, there can be disulfide bond(s) or a chemical cross linker to hold the components of the complex together for a stronger bond than that specific bond formed between the V3 loop of gp120 and the relevant portion of the Tat protein.

Casselli is cited as teaching the advantage of the Cys22 mutant of Tat as an immunogen. Chang and Borbe are said to teach that the V3 loop of Tat is especially immunogenic. Gzyl is said to teach increasing immunogenicity of Env peptides, for example, by deleting the v1 and v2 variable domains and modifying the V3 loop. Wyatt is said to disclose involvement of the V1.N2 variable loop structure in exposing gp120 epitopes induced by CD4 binding. V2 is said to be involved in partially masking epitopes on the native gp120 monomer.

Applicants respectfully point out that the present claims require complex

formation between the two peptide components via the V3 loop of the gp120 protein or peptide and a Tat protein or peptide comprising the specified region to which the V3 loop binds, but it is important to note that in the prior art mixtures, the V3 loop of gp120 is not exposed and available for binding to Tat, so complex formation by any means is not possible. In other words, although the prior art discloses Tat and gp120 together, in the absence of the exposure of the binding residues of the V3 loop, the only interactions that might (at best) exist between these components are Van der Waals forces, which are too weak to cause complex formation. In the present invention, modelling studies have suggested that non-covalent interactions, including hydrophilic and hydrophobic interactions, exist between specific amino acid residues in the stem part of the V3 loop and some regions of Tat, notably, the N-terminal and cysteine-rich regions of Tat. This is supported by the enclosed data which shows the binding kinetics between different forms of Env and Tat. From this data it can be seen that trimeric Env (spectrum a), trimeric ΔV2 Env (b) and monomeric ΔV2 Env (d) all form complexes with Tat. In all three of these proteins, the V3 loop is exposed and available for binding to Tat. Conversely, monomeric wild-type Env (i.e. gp120) was unable to complex Tat (spectrum c). These results clearly demonstrate that the combination of Tat and gp120, as taught by Voss, would not result in complex formation. Applicants have already amended the claims to remove any confusion over the ability of monomeric wild-type Env to bind Tat (be deleting reference to full length g120) from dependent claims (and despite the fact that the present claims specify **exposure** of the V3 loop). It is believed that the language describing the complex provides the required distinction over the cited reference and makes moot the Examiner's concerns regarding the passage at page 5.

An important feature for the present invention is the V3-mediated complexation of the gp120 protein (or part thereof) with the Tat protein. None of the prior art discloses that the V3 loop of gp120 has to be exposed for complex formation with the Tat protein, or that exposure of the V3 loop will necessarily lead to a complex being formed between said loop and Tat. Furthermore, none of the prior art documents suggest that in order to form a complex with Tat, V3 loop exposure could be achieved either by providing the V3 loop alone, by deleting the V2 loop of

gp120, or by initiating exposure by binding of CD4 to gp120.

Applicants respectfully refer the Examiner to the Specification at page 2, where it is stated:

> Surprisingly, we have found that Tat can interact with the gp120 V3 loop, thereby mimicking the CCR5 co-receptor, both at the molecular (structural) and functional level, thereby conferring on CCR5-tropic HIV strains the ability to infect cell targets expressing only very low amounts of CCR5, and which would not be infected with the same virus input, in the absence of immobilised Tat.

As previously noted, there is no teaching of the necessity of making the V3 loop accessible, nor is there any teaching or suggestion of conditions that would make the V3 loop accessible for binding to Tat in the cited Voss reference. Until the finding that Tat could interact with the V3 loop of Env, mimicking the CCR5 receptor, both at the molecular (structural) and functional levels, no one in the art could have seen any benefit or purpose to using an exposed V3 loop bound to Tat in any immunogenic compositions.

In further support of Applicants' arguments for patentability, there are submitted herewith two scientific publications: Gorny MK, VanCott TC, Williams C, Revesz K, Zolla-Pazner S., *Virology* (2000, Vol 267, pages 220-8) and Fouts TR, Trkola A, Fung MS, Moore JP, Interactions of polyclonal and monoclonal anti-glycoprotein 120 antibodies with oligomeric glycoprotein 120-glycoprotein 41 complexes of a primary HIV type 1 isolate: relationship to neutralization *AIDS Research and Human Retroviruses* (1998, Vol 14, pages 591-7) for the Examiner's consideration Both of these provide evidence that, at the time the invention was made, there was teaching **against** the use of trimeric Env for immunization, based on the observation that oligomers (e.g. trimers) of viral envelope proteins were **less** immunogenic than gp120. Contrary to these teachings, the present inventors (reflecting the core of the invention) have found that trimeric forms of Env, particularly the V2-deleted form, expose residues in the V3 loop that are a target for Tat interaction, while such residues are not exposed in gp120. Accordingly, it is therefore submitted that it would not have been obvious from the teachings of the prior art, at the time the invention was made, for the skilled person to provide a

complex between Tat and trimeric Env having an exposed V3 loop for use in stimulating an immune response against HIV. Moreover, Fouts appears to provide evidence that such a complex might not yield a protective antibody

With respect to the cited Gyzl and Wyatt references, while these may disclose the advantage of various mutants of the Env/gp120 protein and the role of the V2 loop, there is still nothing in these references to suggest that Tat mimics the CCR5 receptor or that Tat binds gp120 via the V3 loop. Gyzl and Wyatt focus on ways to improve the immunogenicity of Env and its cleavage product gp120. The cited Voss references do not teach conditions which would expose the V3 loop or otherwise allow the binding of Tat and gp120 or peptides thereof, and the Gyzl and Wyatt references are focused on Env and do not teach or suggest that the V3 loop of gp120 can bind Tat (or any advantage of such binding). Sattenau teaches that CD4 can induce the exposure of the V3 loop of gp120, but it is silent as to the binding of the exposed V3 loop to Tat. Ibrahim discusses heparin sulfate and Watanabe discusses cross-liking peptides, but neither appears to be germane to the base claims. In the absence of a motivation to expose the V3 loop as relates to binding to Tat, one of ordinary skill in the art would not have been motivated to combine these teachings to arrive at the present invention. There is no indication as to why one would have done so.

Applicants acknowledge that there is a substantial body of prior art related to HIV and potential vaccines. However, no one is believed to have identified the role of Tat as presented in the present application, with its mimicry of the CCR5 receptor and the importance of Tat/Env binding via an exposed V3 loop. Thus, there was no motivation to make the complexes or input components of the complexes, and therefore, the present invention as claimed is not obvious over the cited references. The results obtained with the present immunogenic complex were surprisingly improved, as discussed in the Specification.

Moreover, there is a long felt need in the art for effective vaccines and treatments of HIV, given the difficulty in same, especially vaccines, and this should militate against a finding of obvious over the combination of nine references.

In view of the foregoing, Applicants respectfully maintain that the present invention is not *prima facie* obvious over the cited references and request the withdrawal of the rejection.

Claims 35-50, 52, 63, 64 and 68-72 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Voss et al. (Journal of Virology. 2003. 77:1049-1058) and further in view of Caselli et al. (1999) (J. Immunol. 162:5631-5638, Chang et al. (1999) Vaccine 17:1540-1548, Borbe et al. (1995) J. Peptide Science 1:109-123; Gzyl et al. (2004) Virology 318:493-506, Wyatt et al. (1995) J. Virology 69:5723-5733, Sattenau et al. (1993) J. Virology 67:7383-7393, Ibrahim et al. (1999) Virus Research 60:159-169 and Watanabe et al. (2000) Vaccine 19:1199-1203. Applicants respectfully traverse this rejection.

There is nothing in the cited 2003 Voss scientific reference which teaches or suggests that there should be specific binding between the V3 loop of the Env/gp120 protein or peptide and the Tat protein, via the specific amino acid residues as claimed herein. Neither is the unexpected advantage of the complex as an immunogenic composition taught in this reference. Voss only teaches a combination of components in the vaccine preparation but not a particular complexation to achieve a beneficial result. The remaining references do not provide the required reasonable expectation of success, as argued at length hereinabove.

Moreover, there is a long felt need in the art for effective vaccines and treatments of HIV, given the difficulty in same, especially vaccines, and this should militate against a finding of obvious over the combination of nine references.

In view of the foregoing, Applicants respectfully maintain that the present invention is not *prima facie* obvious over the cited references and request the withdrawal of the rejection.

Claims 43-44 and 46-49 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Debrus et al. (WO 02/087614) as applied to claim 35

above and further in view of Gzyl et al. (2004) Virology 318:493-506, Wyatt et al. (1995) J. Virology 69:5723-5733, Sattenau et al. (1993) J. Virology 67:7383-7393 and Ibrahim et al. (1999) Virus Research 60:159-169. Applicants respectfully traverse this rejection.

In the interest of advancing prosecution and without acquiescing to the rejection, Applicants have amended claims 35 and 40 to recite "the first peptide **comprising** the V3 loop of gp120, and wherein the V3 loop is exposed or available and thereby bound to a binding region on the second peptide to form the complex". New claims 69 and 70 also recite this language.

Note that the Specification (page 2, third full paragraph, and page 4, first full paragraph) states that it was a surprising result that Tat interacts with the gp120 V3 loop, where the V3 loop is available to bind a region of the second peptide in the complex as claimed.

As a first matter, and previously discussed, the Debrus reference does not teach or suggest conditions which would make the V3 loop of gp120 accessible for (specific) binding to Tat. In the absence of that accessibility, there can be no such binding. None of the cited references teach the binding of Tat with the V3 loop or the desirability of a complex or a V3-exposed gp120 protein or peptide. The references other than Debrus have been discussed above, and Debrus certainly does not add what those references lack.

Moreover, there is a long felt need in the art for effective vaccines and treatments of HIV, given the difficulty in same, especially vaccines, and this should militate against a finding of obvious over the combination of nine references.

In view of the foregoing arguments and the teachings of the Specification, for example, at page 2, where the inventors state that the binding of the V3 loop of gp120 was unexpected and the long felt need in the art for vaccines against the AIDS virus, Applicants respectfully submit that the present invention as claimed is not obvious over the cited references, and the withdrawal of the rejection must be

withdrawn.

Additional Comment

It has come to Applicants' attention that Example 7 of the present application incorrectly suggests that complex formation occurs between Tat and gp120.

Conclusion

In view of the foregoing, it is submitted that this case is in condition for allowance, and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This Amendment is accompanied by a Petition for Extension of Time (two months) and payment in the amount of $560.00 as required under 37 C.F.R. 1.17(a). It is believed that this amendment does not necessitate the payment of any additional fees under 37 C.F.R. 1.16-1.17. If the amount submitted is incorrect, however, please charge any deficiency or credit any overpayment to Deposit Account No. 07-1969.

Respectfully submitted,
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